REMARKS/ARGUMENTS

In response to the Final Office Action of November 3, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claim 3 has been amended. Claims 1, 3 and 4 are withdrawn from consideration. It is understood that claims 1, 3 and 4, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time.

Claims 2 and 5-7 are currently under examination. Claims 1-7 remain pending in the instant application.

No new matter has been added by the amendment to the title made herein.

The title was amended to clarify that the deficiency recited is a deficiency of the ICA69 autoantigen (for support see page 1, lines 10-19 of the instant specification as originally filed).

No new matter has been added by the amendments to the claims made herein.

Claim 3 was amended to correct typographical errors.

Rejection under 35 USC 103(a)

Claims 2 and 5, as presented on September 8, 2005, remain rejected under 35 USC 103(a) as allegedly being unpatentable over Karges et al. (Diabetes 46:1548-1556 1997) in view of Humphreys-Beher (Adv Dent Res 10(1):73-75 1996).

According to the Examiner, Karges et al. is deemed to provide guidance on treatment of NOD mice with the ABBOS mimicry high-affinity peptide, in order to induce T-cell tolerance to ICA69. Further, Karges et al. teaches that administration of the ABBOS mimicry peptide reduced diabetes incidence in NOD mice and was able to induce cross-tolerance to the Tep69 epitope of ICA69 autoantigen. The Examiner notes that Karges et al. does not treat the NOD diabetic mice that have primary Sjögren's Syndrome.

According to the Examiner, Humpreys-Beher supplements the guidance of Karges et al. by teaching that the diabetic NOD mouse model also undergoes a corresponding loss in exocrine gland function related to infiltrates symptomatic of the pathophysiology of primary Sjögren's Syndrome.

Based on the guidance provided by Karges et al. on the method of treating diabetes in NOD mice with the ABBOS mimicry high-affinity peptide by inducing tolerance of the mouse's ICA69-specific T cells to ICA69, and the guidance of Humpreys-Beher that some diabetic NOD mice develop primary Sjögren's Syndrome, the

Examiner asserts that it would be *prima facie* obvious to the person of ordinary skill in the art at the time of the invention that treatment of diabetic NOD mice with the ABBOS mimicry high-affinity peptide that induced tolerance in ICA69 specific T cell to ICA69 would also treat any other disease caused by the activity of ICA69 specific T cells, such as primary Sjögren's Syndrome in the same mouse. A practitioner in the art would be motivated to treat NOD mice with diabetes and primary Sjögren's Syndrome with the ABBOS peptide in order to induce tolerance of the mouse's ICA69 specific T cells to ICA69 and thus to treat the diabetes. The person of ordinary skill in the art would have a reasonable expectation of success because the method of Karges et al. treats diabetes in the mouse by inducing tolerance in ICA69 specific T cells and therefore any other diseases caused by these ICA69 specific T cells would also be treated by the induction of tolerance.

Furthermore, claims 6 and 7, as added on September 8, 2005, stand rejected under 35 USC 103(a) as allegedly being unpatentable over Karges et al. (Diabetes 46:1548-1556 1997) in view of Humphreys-Beher (Adv Dent Res 10(1):73-75 1996) and further in view of US 6,207,389 (Dosch et al.).

The Examiner asserts that Dosch et al. supplement the guidance of Karges et al. by teaching an ABBOS sequence, SEQ ID NO:11, that is identical to the instantly claimed SEQ ID NO:2. The Examiner

further asserts that Dosch et al. teach methods for preventing the development of T cell mediated autoimmune disease such as Type I diabetes, in which susceptible subjects are treated with an antigen to prevent the expansion of sensitized T cells.

Applicants respectfully disagree with the Examiner's determination that the claimed methods would be obvious to those of ordinary skill in the art.

The Examiner persists in the belief that treatment of diabetic NOD mice with the ABBOS peptide will also treat any other disease caused by the activity of ICA69-specific T cells, in particular primary Sjögren's Syndrome in the same treated NOD mice. In this regard, the Examiner asserts that Applicants' claimed invention is akin to claiming a method of using aspirin to reduce the risk of blood clots. Since people have been taking aspirin for pain for over 100 years they are at the same time reducing their incidence of blood clots. The methods cannot be separated since they are both dependent only on an inherent property of the aspirin. The Examiner asserts that similarly the method of treating primary Sjögren's Syndrome is dependent upon treating a mammal with ABBOS.

In order to buy into the Examiner's reasoning one would have to believe that the ability to induce tolerance is inherent to the ABBOS peptide and therefore, ABBOS will effectively induce tolerance in any disease involving ICA69-specific T cells.

It has been established that although an inherent feature need not be recognized at the time of the invention, the subject matter must be inherent in the prior art reference (see MPEP 2112 II).

Karges et al. disclose nothing that would suggest that immunotherapy with the ABBOS peptide is generally applicable in the autoimmune disease process. Karges et al. show that neonatal injection of ABBOS had little effect on disease incidence in NOD mice (see abstract, page 1551-52 in the section entitled "Modification of disease course" and Figure 5). However, Karges et al. also show that systemic immunization of young NOD females with ABBOS reduces the diabetes incidence and delays disease expression (see abstract, page 1551-52 in the section entitled "Modification of disease course" and Table 1). Thus, the data of Karges et al. suggests that the ability of the ABBOS peptide to induce tolerance may require optimized conditions.

Furthermore, at the time of the invention, it was known that although the same protein may be targeted in two autoimmune diseases, such as in Type I diabetes and multiple sclerosis, the epitopes targeted may be different (see page 2839, right column, last full paragraph of Winer et al. The Journal of Immunology 166:2831-2841 2001; reference 1). Although activity of ICA69-specific T cells may be found in two diseases, treatment of the diseases with the ABBOS peptide would not be effective if the T

cells were specific for an ICA69 epitope other than Tep69.

Thus, contrary to the Examiner's reasoning, the ability of the ABBOS peptide to effectively induce tolerance in any disease involving ICA69-specific T cells can not be said to be inherent in the prior art.

One can also consider that the ability of the ABBOS peptide to mimic the T cell self-epitope Tep69 of ICA69 is the "inherent property" that enables its effective use in immunotherapy of primary Sjögren's Syndrome. In order to buy into this reasoning one would have to believe that the antigenic mimicry of the ABBOS peptide will function to produce the same result in all instances of use. However, at the time of the invention, this was known not to be true. Winer et al. (The Journal of Immunology 168:475-482 2002; reference 2)teach that the demonstration of antigenic mimicry does not per se imply a primary mechanism for loss of tolerance as the functional outcome of mimicry is affected by both endogenous and exogenous antigen; see page 480, right column, last paragraph to page 481, left column, continued paragraph from page 480). Thus, it is oversimplifying the process of autoimmunity to assume that because immunotherapy with the ABBOS peptide is successful in one autoimmune disease involving ICA69 it will be successful in treating all other autoimmune diseases involving or potentially involving ICA69.

In 1993, the Federal Circuit reversed the rejection in *In re Rijckaert* because the alleged inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art (see MPEP 2112 IV).

Akin to the reasoning of the rejection in *Rijckaert*, the instant rejection depends upon an inherent result which assumes that because ABBOS treats one disease it inherently treats all others (involving ICA69-specific T cells). However, it was known at the time of the invention, that effectiveness of immunotherapy of Nonobese Diabetic Mouse Prediabetes with ABBOS was dependent upon many variables; such as peptide dose, MHC affinity and target self-antigen expression (see attached article of Winer et al. The Journal of Immunology 165:4086-4094 2000; reference 3). These variables were tested until an effective therapeutic protocol for NOD prediabetes was found. Considering that these protocols went through a period of "trial and error" optimization, one of ordinary skill in the art would not be likely to believe that the same protocol can be used as is for successful treatment of any other disease. Thus, as in *Rijckaert* in the instant rejection the alleged inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art. Such reasoning is insufficient to support the instant rejection. Even though one may be able to optimize the protocol of Winer et al.,

it is still not sufficient to establish the inherent effectiveness of the ABBOS treatment since it is only a result that may occur in the prior art (see MPEP 2112 IV).

Furthermore, the observations of the instant inventors, in several ways, were unexpected. For example, at the time of the invention organ-selective autoimmune diseases were known to be characterized by broad spreading to multiple target antigens, and thus the genetic removal of any one such antigen was not expected to be associated with significant disease impact. In autoantigen gene knockouts such as GAD65, ICA69 and IA2 little significant disease impact was found. However, the surprising effectiveness of the claimed ABBOS immunotherapy sets primary Sjögren's Syndrome apart from other autoimmune disorders as it suggests that autoimmunity in this disease is considerably more narrow with less antigen spreading (see the instant specification as originally filed at page 3, line 21 to page 4, line 5 and page 5, lines 9-17).

Furthermore, the claimed immunotherapeutic methods proved to be effective even in late stage disease (see instant specification as originally filed at page 5, lines 5-8) which was also unexpected since prior immunotherapeutic methods using ABBOS for treatment of diabetes in NOD mice were known to be effective only in the early, prediabetes stages (see introduction at 4086 of Winer et al. The Journal of Immunology 165:4086-4094 2000; reference 3).

Thus, the claimed methods exhibited the presence of unexpected properties (significant disease impact with removal of one antigen even in late stage disease) which are evidence of nonobviousness (see MPEP 716.02(a)III).

The Examiner asserts that no hindsight is required to make the following assertion: When the ABBOS peptide is used to treat the NOD mice of Karges et al., it obviously also treats any other diseases mediated by ICA69-specific T cells in these NOD mice, such as primary Sjögren's Syndrome. The Examiner further notes that "any judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time that the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin* 170 USPQ 209

Applicants respectfully disagree with the Examiner's determination.

As stated in the previous Response filed on September 8, 2005, prior to the instant invention, the ICA69 autoantigen was not known to be involved in primary Sjögren's Syndrome, i.e. primary Sjögren's Syndrome was not known to be caused by the activity of T cells specific for the ICA69 autoantigen. The Examiner is reminded that obviousness cannot be predicated on what is not known

time an invention is made (see MPEP 2141.02). Furthermore, the prior art must suggest the desirability of combining the teachings of the cited references (see MPEP 2143.01). Without knowledge of a connection between ICA69 and primary Sjögren's Syndrome, one of ordinary skill in the art would not be able to ascertain any advantages for modifying the teachings of the cited references (Karges et al., Humphreys-Beher and Dosch) to treat primary Sjögren's Syndrome in NOD mice by induction of tolerance to ICA69 and therefore, would not have any motivation to make these changes. In other words, one would not have any reason to treat a disease by creating a deficiency in a protein that it is not known or suggested to be involved in the disease. The Examiner does not cite any reference showing that a connection between ICA69 and primary Sjögren's Syndrome was known prior to or at the time of the invention, thus, the Examiner must have used the information provided in Applicants' disclosure to combine the teachings of the cited references (Karges et al., Humphreys-Beher and Dosch).

A connection between ICA69 and primary Sjögren's Syndrome was unknown prior to the invention, thus the prior art cannot suggest the desirability of combining the cited references to arrive at the instant invention. Accordingly, Applicants assert that the Examiner's arguments are based upon impermissible hindsight, and thus, are not sufficient to support the instant rejection.

Since neither the cited references nor the knowledge available to those of skill in the art at the time of the invention teach any connection between the autoantigen ICA69 and primary Sjögren's Syndrome; one of ordinary skill in the art would have no reason to expect success in treatment of primary Sjögren's Syndrome by induction of tolerance to ICA69 because the ICA69 autoantigen was not known to be part of the pathogenesis of primary Sjögren's Syndrome.

It has been established that the cited references (Karges et al., Humphreys-Beher and Dosch) do not teach or suggest all of the limitations of claims 2 and 5-7 since neither reference connects the pathogenesis of primary Sjögren's Syndrome to the ICA69 autoantigen.

In light of all of the above remarks and those made in the previous response filed on September 8, 2005, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and further contend that a practitioner of ordinary skill in the art, having the cited references (Karges et al., Humphreys-Beher and Dosch)in front of him/her would not have the information and motivation necessary to arrive at Applicants' invention.

Thus, it is respectfully submitted that the combination of the teachings of Karges et al., Humphreys-Beher and Dosch fails to

reasonably teach or suggest to one of ordinary skill in the art that elements of Applicants' processes as specifically set forth in claims 2 and 5-7 as presented herein.

Accordingly, Applicants respectfully submit that the claimed processes distinguish over the prior art and respectfully request that this rejection of claims 2 and 5-7 under 35 USC 103(a) now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendment to the specification and amendment to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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